Remarks

Claims 65-68 and 73-85 are pending in the subject application. By this Amendment, Applicants have amended claim 74 and added new claims 86-87. Support for the new claims can be found throughout the subject specification and in the claims as originally filed (see, for example, original claims 6-20). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 65-68 and 73-87 are currently before the Examiner (with claims 66, 67, 76 and 77 standing withdrawn from consideration). Favorable consideration of the pending claims is respectfully requested.

Applicants would like to thank the Examiner for the courtesy of the telephonic conference conducted with Applicants' undersigned representative on May 14, 2009. The remarks set forth in the Interview Summary Form dated June 3, 2009 are consistent with the substance of that interview. Applicants respectfully submit that the amendments to the claims and the remarks presented herein are in substantial accordance with the substance of the telephonic conference with the Examiner.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08, and a copy of the Lapointe *et al.* reference listed herein. Applicants request that the reference in the IDS be made of record in the subject application.

Claims 65, 68, 73-75 and 79-85 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. Applicants respectfully assert that the claims as filed are enabled. The Office Action in this matter essentially reiterates the previous position of the Office Action and indicates that the arguments submitted with the response of March 11, 2009 have been found unpersuasive. Particularly, the Office Action argues that post filing references provide further evidence regarding unpredictability with respect to the role of PRF1 (also known as REDD1, RTP801 and HOG18) in proliferative disease (citing to DeYoung *et al.* for a teaching in LaPointe *et al.* (*Proc. Natl. Acad. Sci.*, 2004, 101(3):811-816). The Office Action also identifies a number of other references that indicate that REDD1 over-expression was associated with a number of tumors and cancers (such as cervical cancer and metastatic prostate carcinoma (Office Action at page 8).

In this regard, Applicants respectfully submit that those skilled in the art, at the time the invention was made, would have not had a basis to doubt the teachings of the as-filed specification which clearly teach that the inhibition of PRF1 (also known as REDD1, RTP801 or HOG18) was able to inhibit the metastasis of prostate carcinoma cells and reduce or inhibit the growth of tumors arising from prostate cancer cells. For example, the as-filed specification provides a number of Examples demonstrating that tumor volume and metastasis can be reduced in both *in vitro* and *in vivo* assays that were art recognized for such testing. As noted in Examples 5, 9 and 10, the inhibition of PRF1 resulted in a reduction in tumor growth and lymph node metastasis in an orthotopic mouse model (Example 10 and Figure 6) and reduced growth in Matrigel assays (Example 5 and Figure 5). As noted above, a number of post-filing date references have identified over-expression of PRF1 and associated this over-expression with tumorigenesis and/or metastasis (see, for example, Riggins *et al.*, Monahan *et al.* and Faris *et al.* (cited at page 8 of the Office Action)).

With respect to the teachings of DeYoung *et al.*, Applicants have reviewed the LaPointe *et al.* reference and have been unable to find any basis for the alleged teaching that REDD1 expression patterns were substantially the same in a subset of prostate carcinoma specimens. Particularly, Applicants have been unable to identify any mention of PRF1 (or its aliases REDD1, RTP801, DDIT4, DIG1 or HOG18) in LaPointe *et al.* Should the Patent Office be able to identify support for the teachings asserted by DeYoung *et al.* to exist within the within the LaPointe *et al.* reference, Applicants respectfully request the Examiner to identify the specific location of such teachings.

Turning to the other basis for maintaining the rejection of record, Applicants respectfully submit that those skilled in the art would have been able to deliver nucleic acids to target tissues via systemic delivery in view of the state of the art at the time the invention was made. Applicants note that the Office Action acknowledges that systemic delivery of nucleic acids to target tissues had been accomplished around the time the priority application for this matter was filed (*e.g.*, WO 00/44895, WO 01/75164, Devroe *et al.* and Ogris *et al.*). While the Office Action argues that the as-filed specification provides no guidance for systemic delivery that was not available in the prior art, Applicants submit that this is not a proper basis for holding that the presently claimed invention is not enabled.

Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed (see M.P.E.P. §2164.02). Additionally, the specification need not disclose what is known to those skilled in the art and preferably omits that which is known to those skilled in the art and already available to the public (*In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)).

As noted previously, targeted non-viral gene delivery systems such as those discussed in Ogris *et al.* (*DDT*, 2002, 7(8):479-485; a reference available prior to the filing date of the instant invention) provided suitable delivery systems for delivering nucleic acids to target cells. Indeed, a number of both viral based and non-viral nucleic acid delivery systems were known to those skilled in the art at the time the invention was made (see also Devroe *et al.*). The delivery systems of Ogris *et al.* utilized nucleic acid condensing agents and Ogris *et al.* also indicated that strategies existed for reducing non-specific interactions of the polycationic carrier/nucleic acid complex with blood components and to enable the circulation of complexed nucleic acids in the bloodstream. These strategies included "shielding" the complex surface with hydrophilic polymers, such as (poly)ethylene glycol (PEG), (poly)hydroxypropylmethacrylamide (pHPMA) or (poly)vinylpyrrolidine (see page 481, column 1).

Ogris *et al.* further teach that the non-viral drug delivery systems discussed could be actively targeted to specific cells via a variety of targeting agents (including transferrin, EGF and antibodies specific for cell surface markers (page 481, column 2 and Table 1)) ***via systemic administration***. For example, a PEI and transferrin system, with complexes shielded with PEG was used to systemically provide nucleic acids to a target cell. Another system used a liposomal system known as a stabilized plasmid–lipid particle (SPLP), which contained PEG as a shielding agent, enabled circulation of the particles in the bloodstream for >6 h after systemic tail-vein injection and tumor-targeted gene expression in subcutaneous growing B16 mouse melanoma. Yet other systems such as a lipid-based particle and transferrin as both the shielding agent and the targeting agent; a polyplex system based on a linear PEI derivative shielded with transferrin; and another polyplex system based on PEI and using EGF as a targeting agent successfully delivered (systemically) nucleic acids to HUH7 hepatoma established in nude mice. Finally, a delivery system that combined both polycationic carrier molecules (which condense DNA within an inner core) and cationic lipid (which coats the

core's surface with a lipid film) enabled the efficient delivery of therapeutic genes to ovarian carcinoma after tail-vein (systemic) injection in nude mice (see page 482, column 2 through page 483, column 1 "Predominant gene expression in tumors"). Thus, it is respectfully submitted that one skilled in the art, at the time the invention was made, would have been able to practice the subject invention without undue experimentation and reconsideration and withdrawal of the rejection is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachment: Supplemental IDS